

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

I. Status of the claims

Claims 1-6 were cancelled previously. Claim 8 is cancelled in this response without prejudice or disclaimer thereof. Claim 7 has been amended in keeping with the Examiner's suggestions. Exemplary support for the amendments can be found in the specification, for example, in the published application, at page 2, paragraph [0019]; and at page 6, paragraph [0077]. Claim 9 has been amended with support in the specification, for example, at page 3, paragraph [0037], of the published application.

Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 7 and 9-18 will be pending.

II. Statement of the Substance of the Interview

Applicants thank Examiner Winston Shen and Examiner Valerie Bertoglio for the courtesies extended and for their helpful comments during a telephonic interview with Applicants' representative on April 30, 2008.

During the interview, the amendments to claim 7 were discussed. Examiner Shen and Bertoglio agreed with the proposed claim amendments in general and requested Applicants submit the amendments in a response to be considered.

Rejection of claim 8 under section 103(a) over the cited art was also discussed. Since claim 8 is cancelled with its recitations incorporated into claim 7, the arguments below are applied to claim 7. The Examiners confirmed that a declaration in support of unexpected results would be considered upon submission.

II. Claim Objection

The Examiner objected to claim 7 for the informality of missing the word “in” in front of the phrase “the ribonucleotide reductase gene.” Claim 7 has been amended according to the Examiner’s suggestion, thereby obviating the basis of the objection.

III. Rejection of Claims under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 7-18 for alleged lack of enablement. Applicants respectfully traverse the rejection.

The Examiner’s position is that the specification does not support expression of *any* desired protein or *any* alteration, including silent mutations, in the genome of mutant herpes simplex virus (HSV). See section 4 of the Office Action, in particular, the paragraph bridging pages 4 and 5.

Claim 7 has been amended to specify that the desired protein is a cytokine that is capable of eliciting immune response in a tumor cell and that the mutations result in a lack of function of each gene product of the γ 34.5 gene and the ribonucleotide reductase gene. These revisions are supported by the specification (*see* the published application, e.g. at page 2, paragraph [0019]; and at page 6, paragraph [0077]) and in line with the Examiner’s recommendation (Office Action, the paragraph bridging pages 4 and 5). The specification further discloses construction of HSV vectors and impairment of γ 34.5 and ribonucleotide reductase gene expressions (published application, pages 4 and 5). Therefore, one skilled in the art is enabled by the teachings of the specification to make the claimed HSV mutant. Accordingly, withdrawal of the rejection is respectfully requested.

IV. Rejection of Claims under 35 U.S.C. § 103(a)

A. Roizman and Chang

The Examiner rejected claims 7, 9-13, 17 and 18 for alleged obviousness over U.S. Patent No. 6,172,047 to Roizman *et al.* (“Roizman”) taken with Chang *et al.*, *Virology*, 185: 437-440, 1991 (“Chang”). Applicants respectfully traverse the rejection.

The Examiner did not include claim 8 in this rejection, which is a salient admission that claim 8 is non-obvious over Roizman and Chang. Claim 7 has been amended to incorporate the recitation of claim 8. Because neither of these references teach or suggest a mutant HSV that expresses a cytokine capable of eliciting an immune response in a tumor cell, the claimed invention is non-obvious. Therefore, withdrawal of the rejection is warranted.

B. Roizman, Chang and Vile

The Examiner rejected claim 8 for alleged obviousness over Roizman taken with Chang, and further in view of Vile *et al.*, *Ann. Oncol.* 5 Suppl. 4: 59-65, 1994 (“Vile”). Applicants respectfully traverse the rejection.

The Examiner’s position is that, at the time of filing, one skilled in the art was informed by the alleged teachings of (i) Roizman that an HSV with mutant γ 34.5 gene could be used as a therapeutic agent, (ii) Chang that ribonucleotide reductase-negative HSV-1 could be used for gene delivery, and (iii) Viles that injection of cells expressing cytokines in animal could diminish tumorigenicity. Therefore, it would have been obvious to combine these teachings to arrive at the claimed invention.

Applicants respectfully disagree. To reach his conclusion, the Examiner has applied an “obvious to try” rationale that is improper under the statute and governing case law.

The U.S. Supreme Court’s decision, *KSR International Co. v. Teleflex Inc.*, prompted a reconsideration of the obvious-to-try rationale, *i.e.*, positing the obviousness choosing from a

finite number of identified, predictable solutions with a reasonable expectation of success. See the EXAMINATION GUIDELINES FOR DETERMINING OBVIOUSNESS UNDER 35 U.S.C. §103..., published in the *Federal Registrar*, Vol. 72, No. 195 (October 10, 2007), hereafter “the Guidelines.”

Pursuant to the Guidelines, an examiner seeking to advance an obvious-to-try rationale is obliged to articulate:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
- (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
- (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
- (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

If any of these findings cannot be made, then this rationale is unavailable to validate a conclusion that the claim(s) in question would have been obvious, within the meaning of Section 103.

In the present instance, the Examiner has failed to meet the initial burden, pursuant to the Guideline requirements, of establishing a *prima facie* case of obviousness. This is so because, contrary to the Examiner’s contention, there was no reasonable expectation of success in view of the state of art at the time of filing.

The contemporaneous art was hardly one characterized by “a finite number of identified, predictable potential solutions to the recognized ... problem,” namely, the treatment of malignant tumors. To the contrary, the skilled artisan would have encountered a panoply of co-treatments that might be combinable with oncolytic HSV. As the accompanying Rule 132 declaration of inventor Samuel Rabkin demonstrates, moreover, the prior art was replete with publications evidencing a contemporaneous understanding in the field that cytokines, such as IL-1 α , IL-2, IL-3,

TNF, IFN- α , IFN- β , IFN- γ , M-CSF-1 and GM-CSF, *protect* a host from HSV infection and *diminish* replication of HSV in the host cells.*

As Dr. Rabkin attests, this conventional wisdom of the day would have led the skilled artisan away from expressing cytokines in the replication competent HSV for purposes of tumor therapy, as presently claimed, since therapy with such mutant HSV requires HSV to infect and replicate in tumor cells of the host, in order to kill tumor cells. See published application, at page 2, paragraph [0012]. The further alteration of such mutant HSV to express cytokines is done to elicit an immune response against the tumor cell, enhanced by cell killing due to the HSV infection. *Id.* at page 6, paragraph [0077]. Yet, the skilled artisan would have expected that expression of a cytokine to protect the cells from HSV infection and replication, which would diminish the therapeutic effect of the claimed, replication-competent HSV. By the same token, the skilled artisan would not have expected, as the Examiner contends, that combining cytokines with the mutant HSV might result in an enhanced tumor therapy.

The Examiner has advanced no contravening evidence or compelling logic to support the proposition that the skilled artisan would have been motivated to express the cytokines in the mutant HSV. In fact, such a combination runs counter the conventional wisdom at the time of filing. Accordingly, the claimed invention is non-obvious over the cited art, and the subject rejection should be withdrawn.

* Here "infection" is given its common usage, connoting "invasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms." THE AMERICAN HERITAGE® DICTIONARY OF THE ENGLISH LANGUAGE, 4th ed. (Houghton Mifflin Company, 2004), submitted herewith as Exhibit 1.

C. Roizman, Chang, McKay and Wright

The Examiner rejected claims 14-16 for alleged obviousness over Roizman taken with Chang, and further in view of PCT publication No. WO 92/14821 by McKay *et al.* ("McKay") and U.S. Patent No. 5,639,656 to Wright, Jr. ("Wright"). Applicants respectfully traverse the rejection.

Each of claims 14-16 ultimately depends from claim 7. Since, as discussed above, claim 7 is non-obvious over the cited art, it follows that claims 14-16 likewise are patentable of that art. Applicants respectfully request withdrawal of the rejection, therefore.

CONCLUSION

Applicants submit that the present application is in condition for allowance, and they request an early indication to this effect. Examiner Shen is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

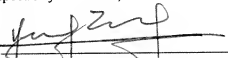
The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then Applicants hereby petition for such extension under 37 CFR §1.136 and authorize payment of the relevant fee(s) from the deposit account.

Date

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